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Method

This invention relates to a novel method of treatment and a novel pharmaceutical composition related thereto.

International Patent Application No. WO 99/18967 describes pharmaceutical compositions for treating chronic and neuropathic pain which comprises an analgesic amount of an opioid and an opioid potentiating amount of a CCK antagonist. WO '967 describes the use of both CCK-A (CCK-1) antagonists and CCK-B (CCK-2) antagonists, although it is described that, generally, CCK-B (CCK-2) antagonists are preferred. Moreover, page 2, lines 6 to 8 of WO '967 describes that CCK-A (CCK-1) antagonists may be suitable, but only at relatively higher dosages.

One specific CCK-A (CCK-1) antagonist which is mentioned in WO 99/18967 is devazepide (Devacade®), which is 3s-(-)-1,3-dihydro-3-(2-indolecarbonylamino)-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one.

Devazepide is commonly administered alongside an opioid analgesic, e.g. such as morphine. However, in normal doses, the commonest side-effects of morphine and other opioid analgesics are nausea, vomiting, constipation, drowsiness, and confusion; tolerance generally develops with long-term use, but not to constipation which is the most common undesirable side effect of morphine treatment.

International Patent Application No. WO 99/18967 specifically describes a pharmaceutical formulation comprising a CCK antagonist, such as devazepide, an opioid and a biphasic carrier, comprising a glyceride derivative organic phase. This application suggests the possible use of a surfactant, especially when the formulation is in the form of an oil-in-water emulsion.

We have now surprisingly found that a method of treatment of a patient requiring analgesia which comprises administering a monophasic form of devazepide which may be prepared with a surfactant. The use of a surfactant is advantageous in that,

inter alia, it improves the powder flow and/or separation properties of solid devazepide and also reduces or mitigates the undesirable side effects of opioid administration, e.g. constipation.

Thus, according to the invention we provide a method of treatment of a patient requiring analgesia which comprises the separate, simultaneous or sequential administration of a therapeutically effective amount of an opioid analgesic, devazepide and a pharmaceutically acceptable surfactant wherein the daily dosage of devazepide is up to 0.7 mg/kg/day.

The method of the invention especially provides a method as hereinbefore described wherein the devazepide and the pharmaceutically acceptable surfactant are in a monophasic form, e.g. solid or liquid form. Preferably, the devazepide and the pharmaceutically acceptable surfactant are in a monophasic form, eg a liquid form or a solid dosage form. The phrase solid dosage form may mean, for example, in tablet form or, preferably in the form of a flowable powder in a capsule. We have found that the use of a surfactant in a solid dose devazepide composition as hereinbefore described has the advantage of mitigating constipation due to the concomitant administration of an opioid analgesic, whilst also improving the physical properties of devazepide in a solid dose formulation.

Any conventionally known pharmaceutically acceptable surfactants may be used in the method of the invention. Such surfactants include, but shall not be limited to, a lipophilic surfactant, a hydrophilic surfactant or a glyceride, or combinations thereof.

When the surfactant is a hydrophilic surfactant, it may be an ionic or a non-ionic surfactant. Examples of non-ionic hydrophilic surfactants include, *inter alia*, alkylglucosides; alkylmaltosides; alkylthioglucosides; lauryl macrogolglycerides; polyoxyethylene alkyl ethers; polyoxyethylene alkylphenols; polyethylene glycol fatty acids esters; polyethylene glycol glycerol fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; polyglycerol fatty acid esters; polyoxyethylene glycerides; polyoxyethylene sterols,

derivatives, and analogues thereof; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; tocopherol polyethylene glycol succinates; sugar esters; sugar ethers; sucroglycerides; and mixtures thereof.

Examples of ionic hydrophilic surfactants include, *inter alia*, alkyl ammonium salts; bile acids and salts, analogues, and derivatives thereof; fatty acid derivatives of amino acids, camitines, oligopeptides, and polypeptides; glyceride derivatives of amino acids, oligopeptides, and polypeptides; acyl lactylates; mono-, diacetylated tartaric acid esters of mono-, diglycerides; succinoylated monoglycerides; citric acid esters of mono-, diglycerides; alginate salts; propylene glycol alginate; lecithins and hydrogenated lecithins; lysolecithin and hydrogenated lysolecithins; lysophospholipids and derivatives thereof; phospholipids and derivatives thereof; salts of alkylsulphates; salts of fatty acids; sodium docusate; and mixtures thereof.

Examples of lipophilic surfactants include, *inter alia*, alcohols; polyoxyethylene alkylethers; fatty acids; bile acids; glycerol fatty acid esters; acetylated glycerol fatty acid esters; lower alcohol fatty acids esters; polyethylene glycol fatty acid esters; polyethylene glycol glycerol fatty acid esters; polypropylene glycol fatty acid esters; polyoxyethylene glycerides; lactic acid derivatives of mono/diglycerides; propylene glycol diglycerides; sorbitan fatty acid esters; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene-polyoxypropylene block copolymers; transesterified vegetable oils; sterols; sterol derivatives; sugar esters; sugar ethers; sucroglycerides; polyoxyethylene vegetable oils; polyoxyethylene hydrogenated vegetable oils; reaction mixtures of polyols and at least one member of the group consisting of fatty acids, glycerides, vegetable oils, hydrogenated vegetable oils, and sterols; and mixtures thereof.

Examples of glycerides include mono-, di- or tri-glycerides. Such triglycerides include, *inter alia*, vegetable oils, fish oils, animal fats, hydrogenated vegetable oils,

partially hydrogenated vegetable oils, synthetic triglycerides, modified triglycerides, fractionated triglycerides, and mixtures thereof.

In an especially preferred embodiment of the invention the surfactant will be capable of improving powder flow of devazepide and may be known to be a therapeutically effective laxative and/or stool softener. Such laxatives and/or stool softeners may, preferentially be ionic surfactants, especially alkyl sulphosuccinates, alkyl sulphates or alkyl ammonium salts.

Thus, in a preferred embodiment of the invention the surfactant may be selected from the group, docusate sodium (dioctyl sodium sulphosuccinate), sodium dodecyl sulphate and tetradecyltrimethyl ammonium bromide.

In a further embodiment of the invention the surfactant may also possess antimicrobial and/or antiseptic properties. Thus, for example, when the surfactant is tetradecyltrimethylammonium bromide, it may, preferentially, be cetrimide (cetrimide is a mixture substantially comprising tetradecyltrimethyl ammonium bromide and small amounts of dodecyltrimethylammonium bromide and cetrimonium bromide).

In the most preferred embodiment of the invention the surfactant is docusate sodium.

The method of the invention may preferentially comprise the use of a composition which comprises one or more fillers. Thus, such fillers may be selected from the group lactose, mannitol, talc, magnesium stearate, sodium chloride, potassium chloride, citric acid, spray-dried lactose, hydrolysed starches, directly compressible starch, microcrystalline cellulose, cellulosics, sorbitol, sucrose, sucrose-based materials, icodextrin, calcium sulphate, dibasic calcium phosphate and dextrose. A preferred filler is starch, e.g. corn starch.

When the method of the invention comprises the use of a composition which includes a filler, the size of the devazepide and filler particles may be the same or

different. However, in a preferred embodiment the sizes of the devazepide and filler particles will differ. Preferentially, the devazepide, surfactant and/or the filler may be of reduced particle size, e.g. by milling.

The devazepide, surfactant and filler may be present as an intimate mixture. However, in a preferred embodiment the filler particles may be coated with the surfactant, the coated filler and devazepide then being formed into an intimate mixture.

The method of the invention wherein the compositions, comprising devazepide, a filler and a surfactant are especially advantageous in that, *inter alia*, the surfactant acts to hinder or prevent separation of the devazepide and the filler. Furthermore, in one embodiment of the invention the surfactant may also have desirable laxative and/or stool softening properties.

The amount of surfactant present in the composition used in the method of the invention may vary, depending upon, *inter alia*, the level of devazepide present, the level of concomitant opioid analgesic administered, etc. Generally, the ratio of devazepide:surfactant may be from 5:1 to 25:1 w/w, preferably from 10:1 to 15:1 w/w, most preferably 12.5:1 w/w.

When the composition used in the method of the invention includes a filler, the composition may generally comprise devazepide and a surfactant, in the ratio as hereinbefore described, with the remainder of the composition being made up with a filler.

A preferred embodiment of the invention comprises a method wherein a composition as hereinbefore described is filled into a capsule. Any conventionally known materials may be used for the capsule, however a preferred material is gelatin.

Thus, for example, in one embodiment of the invention the composition as hereinbefore described may be made up into a capsule formulation, e.g. with a fill

weight of 150 mg ± 5% by weight or 300 mg ± 5% by weight. In the one preferred embodiment, the capsule formulation may comprise 1.25mg devazepide, 0.1 mg surfactant, e.g. docusate sodium, and 148.65 mg of a filler, e.g. corn starch. In a further preferred embodiment, the capsule formulation may comprise 2.5mg devazepide, 0.2 mg surfactant, e.g. docusate sodium, and 297.3 mg of a filler, e.g. corn starch.

According to a further aspect of the invention we provide the use of devazepide in the manufacture of a pharmaceutical composition comprising a therapeutically effective amount of devazepide and a pharmaceutically acceptable surfactant.

The use of the invention is preferentially the use in the manufacture of a pharmaceutical composition wherein the composition comprises any of the aspects of the methods hereinbefore described. The use as hereinbefore described preferentially comprises the use in the manufacture of a pharmaceutical composition in monophasic form.

By the term therapeutically effective amount of devazepide we generally mean an amount of devazepide effective in the enhancement of opioid analgesia.

In the method of the invention a variety of opioids may be used. Thus, the opioid may be selected from those which are effective analgesics and particularly those which need to be administered at relatively high or increasing doses. Examples include morphine, or a salt thereof such as the sulphate, chloride or hydrochloride, or the other 1,4-hydroxymorphinan opioid analgesics such as naloxone, meperidine, butorphanol or pentazocine, or morphine-6-glucuronide, codeine, dihydrocodeine, diamorphine, dextropropoxyphene, pethidine, fentanyl, alfentanil, alphaprodine, buprenorphine, dextromoramide, diphenoxylate, dipipanone, heroin (diacetylmorphine), hydrocodone (dihydrocodeinone), hydromorphone (dihydromorphinone), levorphanol, meptazinol, methadone, metopon (methyldihydromorphinone), nalbuphine, oxycodone (dihydrohydroxycodeinone), oxymorphone (dihydrohydroxymorphinone), phenadoxone, phenazocine,

remifentanil, tramadol, or a salt of any of these. The opioid used in the method of the invention may comprise any combination of the aforementioned compounds. Naloxone is also included within the definition of an opioid. Especially preferred analgesics which may be mentioned are hydromorphone, oxycodone, morphine, e.g. morphine sulphate and fentanyl. In a preferred embodiment of the invention the analgesic is morphine or morphine sulphate. In a further preferred embodiment the opioid is fentanyl or a salt thereof.

In the method of the invention the devazepide and/or the opioid may be administered using any methods conventionally known *per se*. Thus, such methods would include, but shall not be limited to, administration intravenously, intra-arterially, orally, intrathecally, intranasally, intrarectally, intramuscularly/subcutaneously, by inhalation and by transdermal patch. When the devazepide and/or opioid is administered intravenously, it may, for example, be as an intravenous bolus or a continuous intravenous infusion. When the devazepide and/or the opioid is administered subcutaneously, it may for example be by subcutaneous infusion. Preferably, the opioid and/or devazepide are administered intravenously or orally. Oral administration is especially preferred. In a further preferred embodiment the opioid may be administered by a transdermal patch. When a transdermal patch is used, the preferred opioid is fentanyl or a salt thereof.

Thus, in the method of the invention the daily dosage of devazepide may vary depending upon, *inter alia*, the weight of the patient, the method of administration, etc. In patients that are suffering serious disorders, such as cancer patients, the weight of the patient may be very low and therefore the dosage of devazepide consequentially may be low. Preferably, the daily dosage of devazepide may be from 25 μg/kg/day to 0.7 mg/kg/day, more preferably from 50 μg/kg/day to 0.5 mg/kg/day. For oral administration the daily dosage of devazepide may be from 0.07 mg/kg/day to 0.7 mg/kg/day, preferably 0.07 mg/kg/day to 0.29 mg/kg/day. For intravenous administration the dosage of devazepide is preferably 50 μg/kg/day to 0.5 mg/kg/day.

Thus, the expected daily dose of surfactant, which may optionally have laxative and/or stool softening properties, may be up to 0.056 mg/kg/day. Thus, dependant upon the patient, the daily dosage of surfactant may be from 0.4mg to 1.6mg, preferably 0.8mg. Most preferably, the surfactant will be one which posses both laxative and stool softening properties.

In the method of the invention the dosage of the opioid analgesic administered may vary depending upon, *inter alia*, the nature of the opioid analgesic, the weight of the patient, the method of administration, etc. Thus, for example, the dosage of, e.g. an opioid, such as morphine, may be from 5 to 2000mg daily. A particular dosage which may be mentioned is from 10 to 240mg daily. A daily dosage of morphine may be from 5 to 100mg or occasionally up to 500mg.

According to a yet further aspect of the invention we provide a monophasic pharmaceutical composition comprising an amount of devazepide effective in the enhancement of opioid analgesia and a pharmaceutically acceptable surfactant.

Preferably, the devazepide and the pharmaceutically acceptable surfactant are in a solid dosage form. The phrase solid dosage form may mean, for example, in tablet form or, preferably in the form of a flowable powder in a capsule.

The composition of this aspect of the invention is preferentially a composition which comprises any of the aspects of the methods hereinbefore descried.

The devazepide used in the method and/or the composition of the invention is the S enantiomer, preferentially, the S enantiomer wherein the level of R enantiomer, which may be present as an impurity, is not greater than 1.5% w/w.

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